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EXAMINER				
WINTERBERG, NISSA M				
ART UNIT		PAPER NUMBER		
1618				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary

Application No.

10/564,096

Applicant(s)

LIZIO ET AL.

Examiner

Nissa M. Westerberg

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 March 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 - 32 is/are pending in the application.
- 4a) Of the above claim(s) 2, 5, 12 - 32 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 3, 4, 6 - 11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-8508)
Paper No(s)/Mail Date 1/11/06; 5/30/06; 12/19/06
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of group I and species of cetorelix; chitosan; anionic(meth) acrylate copolymes; especially the EUDRAGIT L type; absence of a separating layer and absence of a bipophilic substance in the reply filed on March 3, 2008 is acknowledged. The traversal is on the ground(s) that "restriction is only proper if the claims are independent or patentably distinct and there would be a tenuous burden placed on the Examiner is restriction is not required" (p 3) and that all claims are linked with respect to a formulation that must satisfy a certain relationship cited in the claims that is repsonsible for the activity and that "unit of invention" has to be considered in regards to the independent claims and that it does not matter is a dependent claim itself contains a further invention.

This is not found persuasive because this application is a national stage entry under 35 USC 371 and restriction and species election are determined by the absence or presence of unity of invention. Section 803 of the MPEP, from which Applicant has provided several citations, regards restriction practice for applications under 35 USC 111. Section 1893.03(d) relates to restriction practice for restriction and species election for applications filed under 35 USC 371. For unity of invention to present, the various groups cannot share the same technical feature. The special technical feature must represent a contribution over the prior art. It appears that Applicant may be referring to

unity of invention in paragraph 2 on p 4 of the remarks, but specific arguments as to why the claims of the instant application do represent a contribution over the prior art and that therefore unity of invention is present are not presented.

The requirement is still deemed proper and is therefore made FINAL.

As to the species elected by Applicant, the claims of the instant Application do not recite EUDRAGIT® L type polymers as a polymer for the outer coating. If this species was present in the claim(s), the claim would not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). Therefore, this species election has been interpreted as the election of anionic(meth) acrylate polymers as the outer film coating required in b) of claim 1.

In the Requirement for Restriction/Species election mailed February 1, 2008, the fifth species election was the absence or presence of a lipophilic matrix. In p 3 and the p 1 of the remarks, Applicant has identified this species election as the "bipophilic matrix." The Examiner has treated the election as the absence of a lipophilic matrix.

Claim 5 of the instant application lacks antecedent basis in claim 1 and the substances listed therein are not proteins, peptides or polymers that are the stated components for the inner matrix layer in claim 1. As such, this claim has been withdrawn from further consideration.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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3. Claims 1, 3, 4 and 6 – 11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 5 and 17 – 19 of copending Application No. 12/030377. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1 – 5 and 17 – 19 of '337 are generic to all that is recited in claims 1, 3, 4 and 6 – 10 of the instant application. That is, the claims of the instant application fall entirely within the scope of the claims of '337 or, in other words, the claims of '337 are anticipated by the claims of the instant application. Specifically, the claims of '337 recite a pellet having anionic (meth)acrylate copolymer and a pharmaceutically active substance embedded in a polymeric matrix wherein the active ingredient is not released in significant (less than 10%) in the stomach and having certain physical (size and friability) parameters. The claims of the instant application recite a multiparticulate pellet formulation in which the pellets comprise an anionic polymer that does not dissolve in the stomach and an inner matrix layer comprised of a peptide or protein active ingredient embedded in a mucoadhesive polymer matrix.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112 1st Paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner was unable to find support for pharmaceutical forms comprising mixtures of the active ingredients listed in claim 10. If Applicant is in disagreement with the Examiner regarding support for the amended claim, Applicant is respectfully requested to point to page and line number wherein support may be found for the instant invention.

6. Claims 1, 3, 4, 6 – 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. None of the derivatives or conjugates meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus of derivatives or conjugates encompassed by the claim. While applicant may act as their own lexicographer, the definition of derivatives given on page 7 of "chemical or biochemical modifications of the

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primary or secondary structure" is insufficient since there is no description of the structural relationship of these derivatives provided in the specification and Applicant has not provided a description as to how the base molecule may be changed while remaining a derivative or conjugate.

Claim Rejections - 35 USC § 112 2nd Paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 3, 4 and 6 – 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In defining the composition of the outer film coating, the phrase "especially" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claim invention. See MPEP § 2173.05(d). The Markush group present in claim 6 also contains "especially", making it unclear what elements are actually being claimed as part of the Markush group.

9. Claims 1, 3, 4 and 6 – 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The amount of active substance present in the pharmaceutical form is defined as "a maximum of 40% by weight of the content of polymer having a mucoadhesive effect." This language seems to imply that

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the polymer is comprised of up to 40% of the active ingredient as a monomer when it appears from section a) of the claim that peptide or protein is merely embedded in a matrix of the polymer and not conjugated to the polymer.

10. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There are no units associated with the average molecular weight of the peptide or protein. The standard unit is generally Daltons (Da) but for peptides and proteins, either Da or more frequently, kDa, are used when stating the molecular weight. It is therefore unclear whether the upper limit of the average molecular weight is 3,000 Da or 3,000 kDa (3,000,000 Da).

11. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner was unable to find any information regarding the active substance "barely" (first item in Markus group, line 1 of p 5 of the claims). Therefore it is unclear what active substance being referred to in the Markush group.

12. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear in what parts of the pharmaceutical form an

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ingredient from the list must be present because of the phrase "wherein the matrix layer additionally matrix comprises".

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1, 3, 6, 7, 8, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. (US Patent 6,465,626).

Watts et al. discloses compositions comprising chitosan, type A gelatin and a therapeutic agent (col 3, ln 7 – 10). The compositions are in the forms of microparticles (col 3, ln 61 – 65), whose diameter are between 1 to 200 μm (col 5, ln 39 – 42). A variety of therapeutic agents, including a number of peptides and proteins some having a molecular weight less than 3,000 Da, are disclosed as suitable for use in the compositions (col 5, ln 65 – col 6, ln 17). Other ingredients such as absorption enhancers can be included in the compositions and compounds which act as absorption enhancers include phospholipids (col 7, ln 64 – 67). The compositions can be formulated in a variety of dosage forms that are familiar to those skilled in the art such as tablets, capsules and pellets (col 6, ln 52 – 67). A tablet or capsule formed using the micropellet results in an oral multiparticulate dosage form.

While the preferred route of administration of the compound is nasal (col 7, ln 5), the compounds can also be administered orally and the pellets adapted for delivery of the therapeutic agent to the small intestine or colon (col 7, ln 10 – 13). This is preferably done through techniques known to those skilled in the art such as coating dosage forms with enteric polymers (col 7, ln 14 – 25). Among such polymers are those polymers sold under the trade name EUDRAGIT® (col 7, ln 22 – 25). The enteric polymer prevents

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release of the therapeutic environment in the stomach which is more acidic, but the coating dissolves upon exposure to the less acidic environment of the small intestine (col 7, ln 19 – 22). The site of delivery may also be controlled by the varying the thickness of the polymer coating (col 7, ln 46 – 49). Page 18 and 19 of the instant specification discloses the monomeric content of various EUDRAGIT® polymers and the composition of the polymers are anionic (meth)acrylate polymers with an anionic monomer content of 5 – 60 wt% and which also dissolve in the pH from 4.0 to 8.0 in the intestine.

In the examples (beginning on col 9, ln 1), microspheres comprised of chitosan, gelatin A and therapeutic peptides (insulin in examples 1 and 2, salmon calcitonin (SCT) in examples 3 and 4 and parathyroid hormone (PTH; example 9) are prepared. The amount of active ingredient present in the composition varies depending on the active ingredient being used and were all well below the 40% maximum amount of active ingredient recited in claim 1 (3.6 wt% for insulin, 0.2 wt% for SCT and 0.4% for PTH). The pH of the layer comprising the chitosan and active ingredient was adjusted to 4 by means of the acid HCl (e.g., col 9, ln 10 – 11). The optimal pH for a particular component depends on the formulation being used and the properties of the active agent being used. For example, if the peptide active ingredient was subject to acid hydrolysis at low pH, a higher pH would be used to mitigate breakdown of the active ingredient during formulation. Thus the pH of a composition is a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of

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ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal pH in order to best achieve the desired results.

As to the viscosity and water uptake of the polymer, chitosan is exemplified by Applicant as a polymer having these properties and components.

A specific example of a peptide with a molecular weight less than 3,000 Da having all the properties as described in the claims was not prepared.

It would have been obvious to one of ordinary skill in the art to prepare a composition as recited in claims 1, 3, 6, 7, 8, 10 and 11 as the various elements and generally conditions are described by Watts et al. as discussed in much greater detail above. The teachings of a document are not limited to the specific examples and the elements of the claims are disclosed by Watts et al., rendering the claims of the instant application obvious.

17. Claims 1 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. as applied to claims 1, 3, 6, 7, 8, 10 and 11 above, and further in view of Berliner et al. (US Patent 5,849,327).

As discussed above, Watts et al. discloses a pharmaceutical composition of pellets comprised of chitosan and a peptide or protein active ingredient. To prevent release of the active ingredient in the stomach, an enteric coating may be applied and the thickness of the layer varied to alter the location in which the active ingredient is

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released by altering the time it takes to dissolve the enteric and expose the layer containing the active ingredient.

Watts et al. does not disclose the physical thickness of the layers that can be applied.

Berliner et al. discloses a oral dosage forms that are coated with an enteric coating (abstract). The coating thickness may vary but in general, coating thicknesses of about 0.1 to about 1.0 mm (100 μm – 1,000 μm) provide the best results (col 4, ln 66 – col 5, ln 3).

It would have been obvious to one of ordinary skill in the art to apply an enteric coating of the thickness of 100 μm – 1,000 μm taught by Berliner et al. to the compositions taught by Watts et al. which comprise chitosan, a protein or peptide active ingredient and an enteric coating. Watts et al. discloses that such coatings are well known to those skilled in the art (col 7, ln 14 – 16) and that variations in the thickness of this layer alter the portion of the digestive system in which the active ingredient is released.

18. Claims 1, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. as applied to claims 1, 3, 6, 7, 8, 10 and 11 above, and further in view of Engel et al. (5,773,032).

As discussed above, Watts et al. discloses a pharmaceutical composition of pellets comprised of chitosan and a peptide or protein active ingredient. To prevent release of the active ingredient in the stomach, an enteric coating may be applied and

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the thickness of the layer varied to alter the location in which the active ingredient is released by altering the time it takes to dissolve. A variety of therapeutic agents are disclosed including LHRH (luteinising hormone releasing hormone) and analogs such as nafarelin, buserelin, leuprolide and goserelin (col 6, ln 3 – 5). The exemplified compounds are short (≤ 10 amino acids) peptidic analogs of LHRH.

Watts et al. does not explicitly disclose cetorelix as suitable therapeutic agent.

Engel et al. disclose the decapeptide cetorelix as a LHRH antagonist (analog; col 1, ln 25 – 26; col 2, ln 1 – 4). Also listed as a LHRH antagonists are goserelin (col 1, ln 33 – 34) and leuprolide (col 1, ln 42 – 43).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare a composition comprising a therapeutic active agent and chitosan and coated with an enteric polymer layer as taught by Watts et al. using cetorelix as the therapeutic agent as cetorelix is taught as LHRH analog by Engel et al. The substitution of cetorelix as the active ingredient is obvious because Watts et al. discloses the genus of compounds to which cetorelix, as well as specific peptidic compounds of the same length as cetorelix, as suitable for use in the composition.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8 a.m. - 4 p.m. ET. If

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attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

NMW